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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,629	06/19/2001	Peter H. St. George-Hyslop	1034/1J800US1	3866

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/18/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/884,629	ST. GEORGE-HYSLOP ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-24 and 26-37* is/are pending in the application.

4a) Of the above claim(s) *8-23 and 29-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,24,26-28,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-final Action of March 22, 2006 on September 22, 2006.

Claims 2, 25 are cancelled. Claims 1, 3, 8-10, 24, 29 are amended. Claims 8-23, 29-35 are withdrawn.

Claims 1, 3-7, 24, 26-28, 36, 37 are under consideration.

It is noted that the Examiner of record has changed.

Withdrawn Objection/Rejection

Specification

Applicant's arguments, see page 20 of Applicant's response, filed September 22, 2006, with respect to the objection to the title have been fully considered and are persuasive. Applicant has provided an amendment to the title. The objection of the title has been withdrawn.

35 U.S.C. § 103(a)

Applicant's arguments, see page 22-25 of Applicant's response, filed September 22, 2006, with respect to the rejection of claims 1, 2, 4, 6, 7, 24, 25, 27, 28 have been fully considered and are persuasive. Applicant indicates that Hisao et al. teach away from the claimed invention and indicates that Hisao et al. teach that, "it is unnecessary to use a coding sequence derived from an APP gene with a mutation at the 717 locus (col. 12, lines 34-30), Applicant's response, page 24, 3rd parag. The rejection of claims

1, 4, 6, 7, 24, 27, 28 has been withdrawn. It is noted that the rejection of claims 2 and 25 are withdrawn as the claims are cancelled.

New/Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-7, 24, 26-28, 36, 37 are newly rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at http://uspto.gov/web.menu.utility.pdf, the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to a transgenic mouse comprising in its genome, a transgene construct comprising a nucleotide sequence operably linked to a promoter encoding a heterologous amyloid precursor protein 695 (APP695) polypeptide wherein the lysine residue at position 670 is substituted by asparagine, the methionine residue at position 671 is substituted by leucine, and the valine residue at position 717 is substituted by phenylalanine, and wherein said promoter directs central nervous system or neuronal expression of said transgene. The claims are also drawn to methods of making the claimed mouse. The specification identifies the following uses for the claimed mice: 1) use in characterization of the pathogenic mechanisms of Alzheimer's disease and 2) use in the development of diagnostics, therapies, and therapeutic compounds (specification, page 1, under "Field of the Invention"). Regarding the nucleic acid sequence and vector (e.g. claims 27, 28), the specification only provides a

single use for these products, which is their use to produce the claimed mouse. Thus, the utility nucleic acid sequence and vector depends on the utility of the claimed mouse.

In regards to asserted utility 1), as identified above, the specification fails to demonstrate that the claimed mouse is a model of Alzheimer's disease. While the specification teaches neuropathological and behavioral changes in the claimed mice (specification, pages 22-23), nothing in the art or specification teaches that there are any Alzheimer's patients who express amyloid precursor protein (APP) with both the K595N/M596L (Swedish) and V642F (Indiana) mutations (i.e., "$APP_{Sw,Ind}$"). Subsequently, because there are no patients with this etiology, it is not readily apparent how the claimed mouse is a model for any human disease. Because the claimed mouse is not a model for a human disease, the asserted utility 2), as indicated above, is not readily apparent.

Since the specification does not assert a specific and substantial utility that meets the requirements of 35 U.S.C. 101 for the claimed mice, nucleic acid sequences, and vector used to make the mice also lack a specific and substantial utility. It is also noted that the method of making the claimed mouse also lacks utility as the method of making the claimed mouse does not result in any mouse that has a readily apparent utility.

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the transgenic mouse, nucleic acid sequence, or vector encompassed by the claims to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7, 24, 26-28, 36, 37 remain rejected in modified form under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As discussed above, while the specification teaches that a transgenic mouse expressing human APP comprising the Swedish and Indiana mutations exhibit neurological and behavioral phenotypes (specification, pages 22-23), nothing in the specification or the art provide guidance that the claimed mouse is a model of human disease. That is, nothing in the art or specification provides guidance that any there is any human disease associated with human APP695 comprising both the Swedish and Indiana mutations. As such, because no human has disease with this etiology, the claimed mouse is not a model of any human disease and has no readily apparent use.

In addition to this issue, the claims are broadly drawn to the use of a heterologous APP695 comprising the Swedish and Indiana mutations (i.e., $APP_{Sw,Ind}$). This means that APP from any species of animal (other than mouse) can be used to arrive at the claimed invention. As a first issue, an artisan cannot rely on the amino acid residue number as being the amino acid to mutate, as not all APP amino acid sequences from other species of animals have the same residue numbers. Further, the specification provides no guidance as to how to identify corresponding residues in proteins from heterologous animals. For example, in a BLAST search using the human amino acid APP sequence (Genbank gi number: 871360) identified a Xenopus APP sequence wherein the numbering of amino acid residues are not the same as that of the human sequence. BLAST [online], 2006 [retrieved on 2006-12-07]. Retrieved from the Internet:< URL: <http://www.ncbi.nlm.nih.gov/BLAST/Blast.cgi>, 2 pages. Second, at

the time of filing, the art teach that not all heterologous proteins expressed in transgenic animals predictably have activity. For example, Hammer et al. 1986, J. of Anim. Sci., 63: 269-278 teach that while transgenic mice that overexpressed human growth hormone exhibited enhanced growth, transgenic pigs that expressed human growth hormone did not increase weight gain (Hammer et al., page 276, under "Effect of Foreign GH on Growth"). As this issue applies to the instant invention, an artisan cannot reasonably predict that heterologous proteins will have predictable activity in transgenic mice. As such, while the specification teaches that the use of human $APP_{Sw,Ind}$, in transgenic mice, wherein the mice exhibit specific neuropathological and behavioral phenotypes (specification, pages 22-23), the specification does not provide guidance for an artisan to use $APP_{Sw,Ind}$ from other species of animals and predictably arrive at specific phenotypes.

The claims are broadly drawn to a promoter that directs central nervous system (CNS) or neuronal expression. At the time of filing, the art teaches that not all neural promoters in transgenic mice behave the same and subsequently, an artisan cannot reasonably predict that one can arrive at the claimed mouse using any neural promoter. Andra et al., 1996, Neurobiology of Aging, 17: 183-190 teach that several neuron-specific promoters were used to drive expression of human APP in transgenic mice. Only the Thy-1 promoter yielded transgene expression levels comparable to or above the endogenous mouse levels (Andra et al., abstract). While the specification teaches the use of a Syrian hamster prion protein gene promoter (specification, page 4, 4th parag.), the specification does not provide guidance for an artisan to use other neural-

specific promoter, such that an artisan arrives at the claimed mouse, wherein the mouse exhibits particular phenotypes.

The claims broadly encompass the use of any strain of mouse. However, at the time of filing, the art teaches that an artisan cannot predictably arrive at the claimed invention using any strain of mouse. Carlson et al., 1997, Human Molecular Genetics, 6: 1951-1959 teach that concentrations of APP that produce amyloid plaques in outbred transgenic lines are lethal for inbred FVB/N or C57BL/6J mice (Carlson et al., abstract). As such, the art teaches that the genetic background in mice can result in widely different phenotypes. While the specification teaches the use of C3HxC57BL6 mice (specification, page 20), the specification does not teach the use of other strains of mice such that an artisan could arrive at the mice exhibiting the phenotypes described in the specification (specification, pages 22-23). As such, an artisan is not enabled for the full breadth of any strain of mouse.

To further illustrate the issue of unpredictability in arriving at the claimed invention with regard to selection of mouse strain and promoter, Hisao et al., 1995, Neuron, 15: 1203-1218 teach that transgenic mice that express human APPInd can have widely differing phenotypes. Hisao et al. teach that there are differences in phenotypes between mice disclosed in their publication and those described by another research group (Games et al., 1995). Hisao et al. indicates that the phenotypic differences appear to stem from differences in mouse strain and differences in transgene construct. Games et al. teach that transgene construct was driven by the PDGF promoter; Hisao teach the transgene construct was driven by the Prp promoter.

Hisao et al. teach that whether the differences between the two mice are a result of the mouse strain or the transgene is unclear and thus, determining the underlying factor(s) that cause differences in phenotypes between the mice requires further research (Hisao et al., page 1213, 2nd col., parag. under "Other Transgenic APP Paradigms" to page 1214, see also Table 4). Another teaching in the art that illustrates the necessity of using the appropriate promoter and genetic background in a transgenic mouse was described by Chishti, et al., 2001, Journal of Biological Chemistry, 276: 21562-21570. Chishti et al. teach that overexpression of APP above a threshold of about 4x endogenous is a prerequisite for deposition of amyloid plaques in the central nervous system. To avoid the toxic effects associated with these levels of APP overexpression, permissive strain backgrounds and particular APP cassettes were used in their study (Chishti, et al., page 21564, 1st col., parag. under "Creation of TgCRND8 Mice Expressing Mutant APP"). As this issue applies to the instant invention, an artisan cannot readily arrive at the claimed mouse, wherein the mouse exhibits particular phenotypes (e.g. as described on pages 22-23 or the specification) using any strain of mouse and any promoter. As such, the specification does not provide guidance for the artisan to practice the claimed invention for its full breadth.

The claims (e.g. claim 1) encompass mice that exhibit no phenotype. However, nothing in the art or specification provides guidance as to how to use mice with no phenotype.

Applicant's arguments filed September 22, 2006 have been fully considered and they are persuasive in part.

Applicant indicates that a rebuttal to the Written Description rejection is provided (pages 20-22 of Applicant's response). However, the rejection that was made (Office Action, March 22, 2006, pages 4-6) was a scope of Enablement and thus, response to Applicant's rebuttal is provided here as follows.

Applicant indicates that the claims have been amended to "transgenic mouse" and thus addresses the issue as it applies to the previous Examiner's scope of rejection being to transgenic mouse (Applicant's response, page 21, 2nd parag.). In response, this amendment addresses the previous Examiner's scope and the rejection is withdrawn.

Regarding the issue of the use of any neural specific promoter in the claimed mice (Applicant's response, page 21, 3rd parag. to page 22), Applicant indicates that the specification describes examples of CNS and neuronal promoters (e.g. specification, page 11, lines 3-7) and has provided a working example of the cosTet prion promoter (specification, page 10, line 24 to page 11, line 2 and Examples 1 and 3). In response, as described above, the art (Andra et al., and Chisti et al.) teach that not all neural promoters have the same level of expression and in particular for Chisti et al., a particular level of expression of APP is required to see plaques in mice. As such, the rejection regarding the broad scope of any neural promoter is maintained.

As such, the claims remain rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 24, 26, 37 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the animal." The scope of "animal" is larger than that of "mouse" that it is unclear whether "animal" was referring back to the mouse or to a different animal. There is insufficient antecedent basis for this limitation in the claim.

Claim 24, step d, uses the phrase, "selecting an offspring where genome comprises..." and appears to be missing the word, "its." Claims 26 and 37 depend on claim 24 and are thus included in the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-7, 24, 27, 28, 36, 37 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Hsia et al., 1999, PNAS, USA, 96: 3228-3233 and as evidenced by Jin et al., 2004, PNAS, USA, 101, 13363-13367 and Selkoe, 2002, Science, 298: 789-791.

Hsia et al. teach a transgenic mouse line (J9) comprising a transgene construct comprising a nucleic acid sequence encoding human amyloid protein precursor (APP) comprising the Swedish (Sw) and Indiana (Ind) mutations operably linked to a PDGF B

chain promoter (Hsia et al., page 3228, 2nd col., 1st parag. under "Transgenic Mouse Lines"). Regarding whether the mice expressed APP695, Jin et al. teach that mice made by Hsia et al. expressed the three human APP isoforms, APP695, APP751, and APP 770 (Jin et al., page 13363, 2nd col., 3rd parag.), and Jin et al. indicate that the Swedish mutation is K670N/M671L and that the Indiana mutation is V717F (Jin et al., page 13363, 2nd col., 3rd parag.). Hsia et al. teach that the PDGF B chain promoter expresses in the brains of mice (Hsia et al., page 3229, 2nd col., 1st parag. under "Age-Related Deposition of A-beta in Neuritic Plaques") and that the APPSw,Ind mice had almost twice as much A-beta in their hippocampi as mice from the APPInd line (Hsia et al., page 3232, 1st col., 1st parag. under "Increasing A-beta Production While Decreasing hAPP Expression Worsens Neuronal Deficits"). Regarding whether the APPSw,Ind mice exhibited an Alzheimer's Disease-related pathology by 3 months of age, Hsia et al. teach that 2-4 month mice exhibited a deficit in synaptic transmission that was twice as large as that in line H6 (i.e., APPInd mice) (Hsia et al., page 3232, 1st col., 2nd parag. under "Increasing A-beta Production While Decreasing hAPP Expression Worsens Neuronal Deficits" and see also Figure 5d). It is noted that the art teaches that loss of synaptic transmission is one characteristic of Alzheimer's disease (e.g. see, Selkoe, in particular, see page 790, "Synapses as the Initial Target in Alzheimer's Disease").

Regarding the claims drawn to methods of making the APPSw,Ind mice, Hsia et al. teach that the transgene (PDGF- APPSw,Ind) was injected into one-cell embryos of mice (Hsia, et al., page 3228, 2nd col., 1st parag. under "Transgenic Mouse Lines").

Thus, Hsia et al. anticipate these claims.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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